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## Prevalence of Metabolic Syndrome in Patients With Psychotic Disorders in the Netherlands

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## Reply to Comments on "Optimizing Early Prediction for Antipsychotic Response in Schizophrenia"

### To the Editors:

We are replying to a Letter to the Editors that commented on our article<sup>1</sup> by Drs Chen et al.<sup>2</sup> There were 2 primary study purposes in our article: the first one was to establish an early prediction model for antipsychotic response in schizophrenia; the second was to propose an appropriate method to evaluate the sensitivity, specificity and/or area under curve values using a logistic regression model (generalized estimating equation method in our article<sup>1</sup>) in repeated measurements study. In our article, we did report that the predictive power for week 6 (0.82) was higher than that observed for week 4 (0.80). This could be because of the use of a pretty small cutoff point of 20% improvement on the Positive and Negative Syndrome Scale, which ended up at a higher response rate on week 6 (57%) than that on week 4 (51%). However, comparing the results of "fitted models" and "simple models" in Table 2 of our article, we indicated that the generalized estimating equation model can get better prediction by incorporating information on early response; otherwise, the results of those 2 models were similar. Also, in Table 2, the results of the Brief Psychiatric Rating Scale simple model, which used only the first week response status to predict the week 4 response, were similar to the values reported by Correll et al<sup>3</sup> (high specificity and low sensitivity).

In Table 1 of their comments, which had baseline characteristics fixed at the same values and varying response status at week 1 or week 2, no difference in predicted response probabilities was observed (Patients 198, 200; Table 1). This is true for all model-based prediction methods, not only for predicting response probabilities (logistic regression model), but also true for predicting Positive and Negative Syndrome Scale total scores (fixed effects' linear regression model). The number of possible distinct predicted values is exactly equal to the all possible combinations of different values contained in the independent variables (or predictive variables) of the fitted model. These phenomena can easily be checked with small sample size and with 1 or 2 independent

variables (better with categorical variables, eg, sex) in the fitted model.

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## Risperidone-Induced Hyperamylasemia, Hyperlipasemia, and Neuroleptic Malignant Syndrome A Case Report

### To the Editors:

The association between neuroleptic malignant syndrome and risperidone treatment, although rare, is a well-documented occurrence. Little has been published, however, on the association between clinical and laboratory markers of acute pancreatitis and the use of risperidone, although such evidence is of some interest.<sup>1–3</sup> Acute pancreatitis caused by risperidone is rare, but is characterized

by high mortality and morbidity rates, as for any drug-induced pancreatitis, where prompt detection of the causing agent and its immediate suspension is fundamental.<sup>1,2,4</sup>

Other studies on pancreatitis and the use of atypical antipsychotics can be found in the literature. These articles show that there is a significantly increased risk of pancreatitis with the use of atypical antipsychotics as opposed to typical ones, such as haloperidol.<sup>2</sup>

Evidence available in the literature also shows that most cases of acute pancreatitis due to atypical antipsychotics occur within six months of beginning therapy.<sup>3</sup> Here is a case of a biochemical hyperamylasemia and hyperlipasemia, together with malignant neuroleptic syndrome (MNS), in a patient treated with risperidone. The clinical features showed up after 2 years of treatment.

### CASE REPORT

A 45-year-old female, with a long-term history of disorganized schizophrenia, was transferred to our clinic from the internal medicine unit of the same hospital. A urinary catheter was placed, and she was fed by nasogastric (NG) tube.

A month earlier, she had been brought to the hospital by a family member because she had developed muscular stiffness, nonspeaking increased, opposition, and food phobia; voluntary bowel or urinary function had ceased, and a rise in body temperature was noted.

Such clinical features were accompanied by a laboratory finding of hyperamylasemia, hyperlipasemia, myoglobinuria, and an increase in creatine phosphokinase (CPK) blood level. At this point in time, besides the raised temperature and reduced motility, there were signs of rhabdomyolysis (liver and kidney functions still being intact) and probable acute pancreatitis.

For this reason, an NG tube and bladder catheter were positioned; an abdominal computed tomography scan was carried out and showed no significant finding and the previously mentioned biochemical markers were checked daily.

During the following days, although myoglobinuria and CPK were progressively reduced to normal levels, amylasemia and lipasemia increased up to a maximum level of 636 U/L (normal range, 5–53 U/L) and 1293 U/L (114–286 U/L), respectively, despite the absence of

any clinical or radiological evidence. A fluctuating temperature was still present.

Because the situation did not require any emergency or short-term medical or surgical intervention, the patient was transferred to our clinic.

During the first days of her stay, she was almost inaccessible to interview, laconic, oppositive, and negativistic, with an overall muscular stiffness and adynamia. She was awake, not very lucid and, apart from the lack of cooperation, she seemed to be oriented toward people but partly confused toward time and space.

Somatic examination was negative. Neurological examination showed an extrapyramidal stiffness, increased by the oppositivism of the patient. From a general clinical point of view, there was still a moderate increase in temperature, with remittent profile. Blood pressure was stable, within normal range; CPK and rhabdomyolysis marker, myoglobinuria, were already within normal range when the patient was transferred to our unit. Amylase and lipase were still high (around the highest level shown above).

The patient was fed for several days through NG tube, the urinary catheter was kept in place and anticoagulant prophylaxis was provided, with low molecular weight heparin subcutaneously.

From the pharmacological point of view, we decided to suspend risperidone, which the patient had been taking for the previous 2 years. We then introduced a therapy based on intravenously lorazepam, in 250 cc saline solution, 3 times a day, converted into an intramuscular preparation, which produced a slow but progressive solution to the muscular stiffness. This confirmed our hypothesis that such a clinical feature was primarily due to MNS from risperidone, rather than being caused by psychopathological syndrome (which, in this latter case, would have been schizophrenia, catatonic type).

The values of amylasemia and lipasemia were progressively reduced, returning within normal range in 20 days. This finding suggested a cause-effect relationship between the use of risperidone and the biochemical features of acute pancreatitis. Radiological examinations (computed tomography scan performed in the internal medicine unit, ultrasound performed during admission into our unit), not showing any morphological sign of pancreatitis, suggest an edematous form of pancreatitis, probably already recovering at that time, as imaging produced no significant finding. The literature already shows evidence of asymptomatic pancreatitis related to another atypical antipsychotic agent, clozapine.<sup>5</sup>

The NG tube was removed at this point, and the patient went back to oral nutrition, beginning with a diet based on easy to swallow food; she also began to be mobilized.

The urinary catheter was removed, bowel training with intermittent catheterization was provided, and the patient was promptly able to regain physiological urination.

Once the general clinical conditions and biochemical markers were stable, we introduced clozapine into the treatment plan, starting with 12.5 mg a day and moving within little more than a month up to 300 mg a day. Such treatment significantly improved the psychopathological outcome, and the patient was discharged.

At an 18-month follow-up, the patient still maintains a good clinical balance; monthly blood tests, including amylase and lipase and blood cell count, mandatory with treatment with clozapine, were negative.

This seems to suggest that the susceptibility to pancreatic dysfunction related to MNS induced by atypical antipsychotics is based on subjective factors, in relation to the specific drug used in treatment, risperidone in this case, rather than to clozapine, which has had more prominence up to now in the literature.<sup>3,5-9</sup>

This case also shows that pancreatic dysfunction may occur even long after the beginning of treatment with atypical antipsychotics. It might then be worth investigating further whether regular long-term monitoring of pancreas function could represent an effective tool for secondary prevention. Early diagnosis and prompt interruption of pharmacological treatment could prevent any further development of severe pancreatitis.

#### AUTHOR DISCLOSURE INFORMATION

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## Toxic Clozapine Serum Levels During Inflammatory Reactions

### To the Editors:

Inflammation-related alterations of drug pharmacokinetics in humans were for the first time published in 1978 by Chang et al,<sup>1</sup> who observed a significantly impaired clearance of theophylline during upper respiratory tract infections. The antipsychotic drug clozapine (CLZ) is liable to a very similar biotransformation and elimination like theophylline.<sup>2</sup> In the last years, individual case reports were published on patients who suffered serious adverse effects due to an increase of CLZ serum concentrations during acute infections.<sup>3-6</sup> To further clarify the question of an association between increased CLZ serum levels and inflammations, we evaluated retrospectively the relationship between pathological values of the inflammatory biomarker C-reactive protein (CRP) and increased CLZ serum levels. We chose CRP as laboratory parameter for an inflammatory process because it is the prototypical acute phase serum protein, rising rapidly in response to inflammation, and is free of diurnal variations as well as age or sex dependency.<sup>7</sup>

All therapeutic drug monitoring (TDM) analyses of CLZ performed in the Department of Psychiatry of the University

**TABLE 1.** CRP Values in Patients With Normal and Elevated CLZ Serum Levels

	Normal CLZ Level (350–600 ng/mL), n = 36 (12 Males, 24 Females)	Elevated CLZ Level (>800 ng/mL), n = 27 (9 Males, 18 Females)	Statistics
N abnormal CRP values (>0.5 mg/dL)	12 (33%)	17 (63%)	$\chi^2 = 5.452$ ; $P = 0.018^*$
N CRP values (>1.0 mg/dL)	3 (8%)	15 (56%)	$\chi^2 = 16.858$ ; $P < 0.001^*$
CRP, mg/dL			
Mean ( $\pm$ SD)	0.69 ( $\pm$ 1.42)	3.64 ( $\pm$ 6.13)	$U = 286.00$ ; $P = 0.005^\dagger$
Median	0.30	1.18	
Range	0.02–6.41	0.04–22.35	

\* $\chi^2$  test. $^\dagger$ Mann-Whitney  $U$  test.

Clinic of Würzburg between 2004 and 2007 were retrospectively screened for CLZ serum levels of more than 800 ng/mL, which is clearly above the recommended therapeutic range (350–600 ng/mL).<sup>8</sup> Subsequently, we checked whether CRP was determined parallel ( $\pm 1$  day) to the TDM. A comparison group was formed by extracting patients with CLZ serum levels within the recommended therapeutic range in whom CRP also had been determined parallel to the CLZ concentration. Clozapine determinations in the comparison group were conducted within the same time period like in the proband group. Both groups were matched as far as possible with respect to age and sex proportion. Patients older than 65 years and patients receiving drugs which are known as inhibitors of the metabolic activity of CYP1A2 or CYP3A4 were excluded in both groups.

The reasons for elevated CRP concerned mostly respiratory or urinary tract infection, but were not recorded systematically. The clinical consequences of the elevated CLZ were also not captured systematically. A relationship with other laboratory parameters like  $\alpha$ -1 acid glycoprotein was not examined.

The frequencies of abnormal CRP values and the mean and median value of CRP among the patients with elevated CLZ serum levels and the patients with serum levels within the therapeutically recommended range were compared.

In total, 27 patients (9 male, 18 female) with an elevated CLZ serum level and 36 patients (12 male, 24 female) with a CLZ serum level within the recommended range could be included. Regarding mean age, mean body weight, sex distribution, applied daily doses, and percentage of smokers, there were no significant differences between both

groups. Data concerning CRP values are displayed in Table 1. Patients with an inflated CLZ level showed significantly more often an abnormal CRP value than patients with a normal CLZ level. The difference became even more apparent if only markedly increased CRP values of more than 1.0 mg/dL were considered. The mean CRP value was significantly higher in the probands with elevated CLZ concentrations than in those with CLZ concentrations within the recommended range. To determine the contribution of the factors age, sex, body weight, dosage, smoking habits, and CRP elevation (>1.0 mg/dL) on the probability of an elevated serum level of CLZ, a binary logistic regression was carried out. With the stepwise forward entry approach, the proposed model only contained CRP elevation. The factors daily CLZ dosage, age, sex, body weight, and smoking habits were not relevant. The predictive probability for this model was 75.4% ( $\chi^2 = 16.6$ ;  $df = 1$ ;  $P < 0.001$ ) after 1 step. Inclusion of further factors did not improve the differentiation.

## DISCUSSION

We found in patients with an increased CLZ serum level significantly more often a pathological CRP value and a significantly higher mean CRP value than in patients with a normal CLZ level. A binary logistic regression revealed CRP elevation as the most relevant predictive factor for an increase of the CLZ serum level. Because we had excluded cases in which any of the concomitant drugs had a known potential for an inhibition of CYP1A2 or CYP3A4, it is highly improbable that drug interactions are responsible for the elevation of serum CLZ concentration.

Elevated CLZ serum levels in connection with an inflammatory reaction or infection are described in several case reports,<sup>3–6</sup> which are in accordance with our findings.

The most obvious explanation for a rise of the CLZ serum level would be a reduction in the activity of the metabolizing enzymes. According to in vitro data, acute infections or inflammations may lead to a compromised drug metabolism which involves various CYP450 subtypes mostly via a down-regulation of their activity mediated by reduced transcription.<sup>9–14</sup> The activity of the specific isoforms CYP3A4 and CYP1A2, which are important in CLZ metabolism, can be affected in this way.<sup>11,12</sup> Several forms of cytokines, namely interleukin 1 $\beta$  and IL6, but also tumor necrosis factor  $\alpha$  and interferons  $\alpha$  or  $\gamma$  can mediate this effect.<sup>11,12</sup> There may also be other mechanisms which can cause elevated cytokine levels with a subsequent rise of CLZ serum concentration via a cytokine-mediated down-regulation of CYP450 enzymes. In some cases, CLZ itself may be the cause of the inflammatory condition by means of a CLZ-mediated hypersensitivity reaction which results in an increased release of inflammatory cytokines.<sup>5</sup>

Altogether our findings suggest that changes in laboratory parameters indicating an inflammatory reaction, especially a rise of CRP, as well as clinical signs of an incipient infection should be seen as sufficient reason to have serum CLZ concentrations determined by therapeutic drug monitoring, as a dose reduction may be required to prevent intoxication and side effects in patients. Up to now, data regarding a possible impact of inflammatory diseases on the biotransformation of other psychotropic agents are nearly completely lacking. Further studies are necessary to address this important question.

## AUTHOR DISCLOSURE INFORMATION

The authors have no conflicts of interest to declare.

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## Predictors of Clinical Worsening After a Switch to Aripiprazole in Patients With Schizophrenia: A 1-Year Naturalistic Follow-Up Study

### To the Editors:

Although the favorable side effect profile of aripiprazole<sup>1</sup> could provide long-term benefits, switching to this medication is not always successful in all patients.<sup>2</sup> Although this phenomenon is seen in all available antipsychotics, different mechanisms may be involved with clinical worsening after a switch to aripiprazole that exceptionally has a partial agonistic activity at dopamine D<sub>2</sub> receptors. Given the unique action of this drug, it would be important to elucidate the time course and predictors of the worsening after the switch from a full antagonist antipsychotic to aripiprazole, which would be expected to help physicians more effectively monitor patients while acknowledging the importance of careful monitoring in every patient. This notwithstanding, there is no investigation that tried to identify predictors of clinical worsening after switching to aripiprazole. We therefore conducted a 1-year follow-up study to examine the time course and potential predictors of clinical worsening following a switch to aripiprazole in patients with schizophrenia.

This 1-year naturalistic follow-up study was conducted at 3 psychiatric hospitals and clinics in Tokyo, Japan. Consecutive inpatients and outpatients aged 18 years and older, who met the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* criteria for schizophrenia and were treated with a stabilized dose of oral antipsychotics for at least 1 month before study entry, were assessed for inclusion in the study, and all eligible patients were approached to participate in the study. The exclusion criteria included the presence of *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition*-defined substance abuse or dependence within the preceding 6

months, serious neurological or uncontrolled medical condition(s), and a treatment history of clozapine.

Aripiprazole was initiated at 12 mg/d, maintained at the same dose for the first 2 weeks, and then titrated between 12 and 30 mg/d until week 52. Previous antipsychotics were reduced biweekly by 25%, whereas other psychotropics were not changed throughout the study period. Participants received monthly assessments, using the Clinical Global Impression: severity of illness (CGI-S).<sup>3</sup> Patients who showed a 1 point or more increase in the CGI-S within 1 year were classified as “worsened group” whereas the others were defined as “stabilized group”. The trial protocol was approved by the institutional review board at each participating site. After full description of the study, all participants provided their written informed consent before entering the study.

Demographic variables were compared between the 2 groups by the Student *t* test or the  $\chi^2$  test, as appropriate. Logistic regression analysis was used to examine predictors of worsening among age, sex, treatment setting (ie, in/outpatient), duration of illness, previous antipsychotic dose, aripiprazole dose, and baseline CGI-S. Baseline antipsychotic doses were converted to daily defined dose (DDD) unit<sup>4</sup> or chlorpromazine equivalents (CPZE) on the basis of a previous report,<sup>5</sup> in which relative potency of each antipsychotic agent was determined based on its clinical efficacy in human clinical trials. When they received 2 or more antipsychotics, the sum of DDD or CPZE was calculated. A 2-tailed *P* < 0.05 was considered statistically significant. Statistical analyses were carried out, using the Statistical Package for Social Science version 16.0 for Windows (SPSS Inc, Chicago, Ill).

Forty patients were enrolled; of these, 16 (40.0%) patients experienced a clinical worsening within 1 year (Table 1). All these worsened patients experienced exacerbation of auditory hallucination and/or delusion. A mean  $\pm$  SD interval between the switch and clinical worsening was  $12.8 \pm 7.1$  weeks (range, 4 to 34 weeks), and it occurred within 17 weeks in more than 90% of the patients (*n* = 15).

The dose of previous antipsychotics was significantly higher in the worsened group than the stabilized group (Table 1). In addition, when patients on risperidone or olanzapine at baseline were separately analyzed, those who experienced a clinical worsening received higher doses (risperidone, mean  $\pm$  SD,  $7.7 \pm 2.9$  mg/d [*n* = 6] vs  $3.3 \pm 1.4$  mg/d [*n* = 8] *P* < 0.01; olanzapine, mean  $\pm$  SD,  $14.4 \pm 5.3$  mg/d

**TABLE 1.** Demographic Characteristics in Clinical Variables\*

	Stabilized Group (n = 24)	Worsened Group (n = 16)
Male, n (%)	15 (62.5)	7 (43.8)
Inpatient, n (%)	13 (54.2)	9 (56.3)
Age, y	53.0 ± 16.6	55.3 ± 16.8
Duration of illness, y	23.9 ± 17.5	28.9 ± 18.3
Previous antipsychotic dose		
DDD, unit	0.87 ± 0.35	1.66 ± 0.72 <sup>†</sup>
CPZE, mg/d	381.8 ± 155.5	726.6 ± 311.4 <sup>†</sup>
Concomitant use of benzodiazepines, n (%)	12 (50.0)	10 (62.5)
Baseline CGI-S	4.1 ± 1.1	4.6 ± 1.0
Aripiprazole dose, mg/d	16.8 ± 3.1	18.0 ± 0.0

Values are shown as mean ± SD.

\*There were no significant differences in all clinical variables except for previous antipsychotic dose between the 2 groups by the Student *t* test or the  $\chi^2$  test.

<sup>†</sup>*P* < 0.05 by the Student *t* test.

[*n* = 9] vs 10.0 ± 3.0 mg/d [*n* = 12], *P* < 0.05). No significant differences were found in other demographic and clinical variables between the 2 groups. A logistic regression analysis found that only a higher dose of previous antipsychotics before aripiprazole was associated with clinical worsening (odds ratio, 1.02; 95% confidence interval, 1.00–1.02; *P* < 0.05). Among those worsened patients, 8 patients were stabilized by a dose escalation (*n* = 6) or a careful course observation alone (*n* = 2). In addition, when these 8 patients were included in the stabilized group, the difference in previous antipsychotic dose between the 2 groups was found in terms of both DDD unit (mean ± SD, 1.71 ± 0.68 vs 1.06 ± 0.59; *P* < 0.01) and CPZE (mean ± SD, 725.0 ± 307.1 mg/d vs 468.4 ± 258.4 mg/d; *P* < 0.05).

## DISCUSSION

A higher dose of previous antipsychotic dose was found to be associated with subsequent clinical worsening after the switch to aripiprazole. One possibility would be that patients who received a higher dose might suffer more severe symptomatology at baseline. Those potentially more severe patients may be more likely to fail to tolerate an antipsychotic switch. However, this possibility could be negated by the fact that no significant difference was found in terms of the baseline CGI-S in the present study. Alternatively, we suppose that a potential difference in the dopamine receptor reserve needs to be considered. Administration of antipsychotic drugs has been reported to lead to an elevation in dopamine D<sub>2</sub> receptors,<sup>6</sup> and the evidence

suggests that this up-regulation may be in the range of 30% to 40%.<sup>6</sup> If this up-regulation could be dose-dependent, patients who have been treated with a higher dose of previous antipsychotics would experience a greater increase in the net dopaminergic transmission after switching to a partial agonist, aripiprazole. This in turn would be expected to result in a clinical worsening. In any case, a more careful observation should be given to patients who receive a relatively high dose of antipsychotics when a switch to aripiprazole is performed.

Out of the 16 worsened patients, 8 patients were stabilized by increasing the dose of aripiprazole or a careful course observation, which means that switching to aripiprazole was not feasible in the remaining 8 (20%) patients. This rate is comparable to that in one retrospective 6-month cohort study in the US (*n* = 444)<sup>7</sup> that showed 20% of outpatients switched to aripiprazole were hospitalized within 6 months. This study also found that a mean time to hospitalization after switching was 65.7 days in aripiprazole, similar to the mean time to worsening of 13 weeks in the present study. These observations emphasized the need of a more thorough monitoring within 3 months after switching to aripiprazole. This period may need to be extended to 4 months because more than 90% of worsened patients experienced a clinical worsening within 17 weeks in this study.

Several limitations should be noted. First, the small sample size limits the interpretation of our results. Second, the minimum duration of receiving stabilized dose of antipsychotics (1 month) in the inclusion criteria might be too short,

which might have included heterogeneous patients. Third, psychopharmacological management for worsened patients was not standardized. Fourth, psychopathology was assessed, using the CGI alone, in this study. Our primary interest was to identify predictors of clinical worsening after switching to aripiprazole in the real-world clinical setting. Although it would have been ideal to perform comprehensive assessments, practical clinical issues limit the extent to which they can be applied in busy clinical practice. Still, taken together with the open-label study design with a small sample size of this study, more methodologically sound studies, using structured comprehensive assessments, in larger samples are needed to better understand predictors of clinical worsening.

In conclusion, the findings of this study suggest that patients who receive a relatively high dose of antipsychotics may have a greater risk of clinical worsening after a switch to aripiprazole and require a more thorough observation within the first 4 months. This has important clinical implications, both in terms of providing safe antipsychotic treatment and understanding potential mechanisms of psychotic decompensation after a switch from a full antagonist antipsychotic to a partial agonist antipsychotic.

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## The Effects of Risperidone on the Cognitive Performance of Individuals With Schizotypal Personality Disorder

**To the Editors:**

Cognitive dysfunction is a core feature of schizophrenia and is present in most patients with the illness, frequently preceding the onset of other symptoms and persisting even after other symptoms have been effectively treated.<sup>1</sup> These abnormalities, which are the best predictor of impairments in various aspects of functional outcome in schizophrenia,<sup>2,3</sup> predict poorer treatment adherence<sup>4,5</sup> and increased tendency for relapse in first episode patients.<sup>6</sup>

Several of the cognitive deficits found in patients with schizophrenia are also present in individuals with other schizophrenia spectrum disorders, such as schizotypal personality disorder (SPD).<sup>7–10</sup> We have previously demonstrated that the cognitive impairments of individuals with SPD are amenable to treatment with pharmacological agents, in particular those that modulate catecholamine functioning. In particular, 4 weeks of treatment with guanfacine, significantly improved the context processing abilities of SPD participants compared with those treated with placebo.<sup>11</sup> In addition, treatment of SPD patients with a low dose of risperidone resulted in a significant reduction in negative and general symptoms over 3 weeks.<sup>12</sup>

There is some evidence that second generation, or atypical antipsychotics, improve the cognitive performance of individuals with schizophrenia.<sup>13,14</sup> Based on these results, we sought to evaluate the impact of risperidone on the cognitive functioning of individuals with SPD. We hypothesized that risperidone would result in improvements in the cognitive performance of SPD participants, in that guanfacine was more effective at reducing cognitive impairments in people with SPD than in schizophrenia.<sup>11,15</sup>

We recruited male or female participants between the ages of 18 and 60 years from the outpatient clinics at the Mount Sinai Medical Center (New York, NY) and the Bronx Veterans Affairs Medical Center (Bronx, NY). Participants were required to meet *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* criteria for SPD. When there was comorbidity with other personality disorders, SPD was judged by to be the primary diagnosis. All patients received a

urine toxicology screen. See our previous publications for the full diagnostic assessment. The study was approved by the institutional review boards at the 2 institutions, and all participants signed a written informed consent statement. Data were collected from 1995 to 2001.

Patients were randomly assigned in a 1:1 ratio to receive risperidone or placebo in identical tablets. All patients received a single-blind 2-week placebo lead-in followed by a double-blind 10-week medication trial. The dosage of risperidone was titrated upward in a stepwise design, beginning with 0.25 mg/d for the first week, 0.5 mg/d for weeks 2 and 3, 1.0 mg/d for weeks 4 and 5, 1.5 mg/d for weeks 6 and 7, and 2.0 mg/d for the remaining weeks. Cognitive performance was assessed at baseline, as well as at weeks 6 and 12. The cognitive assessment battery consisted of measures of a range of neuropsychological functions, including spatial and verbal working memory, vigilance, spatial memory, and word list learning (for a more complete description of these assessments, please see our previous work<sup>7</sup>). For all the dependent variables, we computed change scores from baseline to 6 and 12 weeks. We then conducted a series of univariate analyses of variance comparing the change scores of individuals in our risperidone group to those in our placebo group.

Thirty-one participants entered into the study, 19 of whom were randomized to risperidone and 12 to placebo. Several participants in both groups dropped out of the study for various reasons, such as boredom or fatigue, ostensibly not related to group assignment. Two participants in the risperidone group were withdrawn, 1 because of an increase in suicidal ideation and 1 because of galactorrhea. In total, 9 participants in the placebo group and 11 participants in the risperidone group completed all 12 weeks of the trial and were included in the analysis. The groups did not differ significantly in the number of participants who terminated prematurely (Fisher exact test,  $P = 0.452$ , NS). The groups were also comparable in terms of age, education, sex, vocabulary scores, or block design performance (all  $P$ s = NS). Clinical response to risperidone was previously reported<sup>12</sup> in a sample that included 23 of the 31 participants in the current study; raw scores on the symptom assessment of the current sample are presented in Table 1.

Raw scores for the cognitive assessments at baseline, week 6 and week 12, are presented in Table 1. There were no significant differences between the risperidone group and the placebo group in



**TABLE 1.** Results of Cognitive Assessments at Baseline, Week 6 and Week 12

	Risperidone Group			Placebo Group		
	Baseline mean (SD)	Week 6 mean (SD)	Week 12 mean (SD)	Baseline mean (SD)	Week 6 mean (SD)	Week 12 mean (SD)
PANSS positive	11.9 (4.7)	10.4 (2.8)	9.4 (2.5)	13.1 (5.6)	12.2 (3.5)	12.3 (4.3)
PANSS negative	13.9 (4.7)	12.2 (5.8)	12.1 (5.2)	16.8 (7.8)	16.9 (7.5)	16.0 (6.2)
PANSS general	26.9 (7.7)	23.9 (6.2)	22.1 (5.2)	31.9 (10.6)	32.1 (9.6)	28.9 (9.9)
WMS-VR	33.1 (5.1)	34.00 (5.9)	34.9 (7.1)	32.3 (5.0)	37.5 (0.6)	34.2 (4.1)
WMS-VR LD	29.1 (8.4)	31.6 (7.0)	36.8 (13.5)	29.9 (6.8)	36.5 (1.0)	34.4 (3.9)
WLL trail 5	12.8 (5.3)	14.2 (5.1)	15.7 (5.3)	14.8 (4.9)	16.0 (4.9)	19.5 (3.5)
WLL LD	10.9 (4.2)	12.7 (4.9)	15.7 (6.6)	13.0 (5.4)	14.0 (6.4)	16.8 (5.0)
CPT <i>d'</i>	0.9 (0.5)	1.5 (0.8)	1.3 (0.83)	2.0 (1.3)	2.3 (1.1)	2.3 (1.0)
PASAT	31.0 (5.9)	34.6 (14.3)	36.7 (13.5)	34.6 (11.5)	41.4 (7.3)	44.8 (5.2)
DOT 30 s delay	1.2 (1.4)	1.6 (1.6)	0.91 (0.61)	1.4 (1.3)	1.9 (1.0)	1.4 (1.6)

PANSS indicates Positive and Negative Syndrome Scale; WMS-VR, Wechsler Memory Scale Visual Reproduction Test raw score; WMS-VR LD, Wechsler Memory Scale Visual Reproduction Test 30-minute delay interval raw score; WLL Trial 5, Word List Learning total words recalled at trial 5; WLL LD, Word List Learning total words recalled after 20-minute delay interval; CPT *d'*, signal detection continuous performance test number of errors of omission; PASAT, Paced Auditory Serial Addition Test total number of correct responses; DOT 30s delay, Dot test distance error at the 30 sec delay minus the distance error in the copy condition.

change from baseline on any of the cognitive variables following either 6 weeks, all *F*s < 2.5, all *P*s > 0.15, or 12 weeks, all *F*s < 1.2, all *P*s > 0.28, of treatment.

## DISCUSSION

We hypothesized that individuals with SPD, who frequently demonstrate a similar profile of cognitive impairment to individuals with schizophrenia, would benefit from treatment with risperidone, as they had previously been shown to benefit from other cognitive enhancement therapies. The results of the current study did not support this hypothesis and are not as large as those seen in the generally negative Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial looking at schizophrenia patients and atypical antipsychotics.<sup>16</sup> These data suggest that although antipsychotic medications may reduce clinical symptoms in SPD, they may not have a substantial benefit for cognitive functioning.

There are several possible explanations for our failure to find statistically significant results. The small sample size and high number of drop-outs led to modest power. Furthermore, examination of baseline performance in both groups suggests that the SPD patients were less impaired on cognitive measures than cohorts in our previous studies. Although we failed to find statistically significant differences between individuals with SPD treated with risperidone and those treated with placebo on our cognitive assessments, more severe cognitive impairment in SPD might have responded to risperidone. Future research on other treatments targeting these deficits in SPD

is warranted, especially in those individuals who demonstrate cognitive abnormalities that are closer to the severity of what is seen in schizophrenia.

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medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007;64:633–647.

## Rhabdomyolysis Following Dose Increase of Clozapine and Combination Therapy With Lithium

### To the Editors:

The treatment of refractory psychotic or mood disorders often requires combination drug therapy. We report here on a patient with refractory schizoaffective disorder, who presented with rhabdomyolysis after a dose increase of clozapine and combination therapy with lithium.

### CASE REPORT

Mr A, a 29-year-old Taiwanese man, was initially diagnosed with bipolar disorder at age 16 years. Because of poor control of his mood symptoms and the development of auditory hallucinations, he had been tried on many medications, including carbamazepine, haloperidol, risperidone, and olanzapine. At age 26 years, he was readmitted because of symptoms of schizophrenia. A variety of medications, including ziprasidone, amisulpride, and olanzapine, were then tried but without adequate efficacy. Finally, he was prescribed clozapine (125–200 mg/d).

At age 29 years, he was re-hospitalized because of recurrent florid psychotic and manic symptoms, and his diagnosis was changed to schizoaffective disorder. We gradually titrated the clozapine dose up to 450 mg/d over 5 weeks and added valproic acid which was increased to 2000 mg/d within a month (Table 1). Although his psychotic symptoms improved, his mood symptoms persisted and thus, 8 sessions of electroconvulsive therapy (ECT) were performed between day 43 and day 68. Although improvement was noted, his manic symptoms recurred within 1 week after the end of ECT. Clozapine was increased further to 500 mg/d on day 72. Lithium was added on day 78, and the dose was titrated to 1200 mg/d within a week. Manic symptoms showed partial improvement.

Generalized muscle aches were noted on day 89 (17 days after the clozapine dose increased to 500 mg/d), and laboratory examination revealed increased serum creatine kinase (CK 6776 IU/L). Rhabdomyolysis was the probable diagnosis after excluding infection and neuroleptic malignant syndrome. We reduced his clozapine dose from 500 mg/d to 400 mg/d on day 90. After adequate

intravenous hydration, his physical symptoms and CK levels gradually returned to normal within a week. He was discharged on day 109.

### DISCUSSION

Previous evidence that substance abuse and medical drugs are 2 major causes of rhabdomyolysis in hospitalized patients prompted us to investigate the adverse effects of the anti-psychosis medications administered in this case.<sup>1</sup> Rhabdomyolysis had been documented in case reports involving an overdose of lithium,<sup>2–4</sup> clozapine,<sup>5</sup> or valproic acid.<sup>6</sup> Rhabdomyolysis cases have also been reported in the process of correction of hyponatremia associated with polydipsia and clozapine use.<sup>7,8</sup> Lithium-induced rhabdomyolysis might be related to a hyperosmolar state,<sup>9</sup> or polydipsia-induced hyponatremia.<sup>10</sup>

Clozapine is a potent 5HT<sub>2a</sub> antagonist that might interact with serotonin, leading to passive diffusion of serotonin into skeletal muscle cells. The resultant accumulation of serotonin can be toxic to skeletal muscle cells, resulting in cell necrosis and increased blood CK levels.<sup>11</sup> In this patient, a dose increase of clozapine from 450 to 500 mg/d seemed on its own could induce rhabdomyolysis, judging from the fact that he tolerated clozapine at a dose of 400 mg/d in combination with lithium at a dose of 1200 mg/d after day 90. The role of lithium cannot be completely excluded because a combination of both drugs might theoretically induce pharmacokinetic or pharmacodynamic changes. The interaction between lithium and clozapine and the effect of their interaction on rhabdomyolysis remain unclear. We speculate that the change in serum osmolality associated with lithium might result in changes in the permeability of cell membranes, especially those of skeletal muscle. In this situation, the adjunct use of antipsychotics may cause increased amounts of serotonin to diffuse into cells, causing the breakdown of skeletal muscle. However, serum osmolality, sodium or potassium levels for this patient were not obtained on the day when rhabdomyolysis occurred, so we cannot rule out other explanations.

To our knowledge, this is the first case report in which combined treatment with clozapine and lithium appears to have caused rhabdomyolysis in the absence of a toxic serum level of lithium. Consequently, in addition to monitoring serum levels to maintain below-toxic levels of medication(s), we suggest paying close attention to patient reports of muscle aches and, when necessary, regularly

**TABLE 1.** Summary of Treatment Course and Associated Laboratory Examinations

	Days After Admission																	
	19	29	39	43	52	61	69	72	74	78	83	85	89	90	92	95	99	106
Treatment course																		
Clozapine (mg/day)	300	350	450	450	450	450	450	500	500	500	500	500	500	400	400	400	400	400
Valproic acid (mg/day)	1500	2000	2000	hold	hold	hold	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Lithium, mg/d										600	900	1200	1200	1200	1200	1200	1200	1200
ECT				**	**	**												
				(8 sessions)														
Blood level																		
Valproic acid, $\mu\text{g/mL}$	84.9	89.3	98.24				47.94		82.85			75					84.2	77.55
Lithium, mmol/L											0.27	0.64	0.48		0.41		0.45	0.83
WBC, K/ $\mu\text{L}$		10.13	11.04		7.78	8.31	13.03		10.14			12.03					12.45	11.33
CK, IU/L													6776	3494	1261	222	147	97
BUN, mg/dL													9.8	7.1	6.2	7.3		
Cre, mg/dL													1.1	0.9	1.0	1.2		

WBC indicates white blood cell; BUN, blood urea nitrogen; Cre, creatinine; \*\*, marks of ECT.

checking serum CK levels, serum osmolality, and serum electrolytes, to monitor for rhabdomyolysis during the treatment of refractory psychotic or mood disorders.

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## Prevalence of Metabolic Syndrome in Patients With Psychotic Disorders in the Netherlands

### To the Editors:

Patients with chronic psychotic disorders have an elevated risk for developing cardiovascular and metabolic diseases.<sup>1</sup> The metabolic syndrome is a measure for the clustering of metabolic and cardiovascular risk factors and is frequently used in patients with psychotic disorders.<sup>2,3</sup> So far, no study has been conducted to describe the prevalence of the metabolic syndrome in patients with psychotic disorders in the Netherlands. This study aimed to estimate the prevalence of metabolic syndrome and to compare characteristics of patients with metabolic syndrome to those without.

This cross-sectional analysis of patients with psychotic disorders participating in a disease management program was conducted in the department of psychotic disorders of a mental health care center in the Netherlands between January 2003 and April 2007. As part of the disease management program, patients had yearly assessments of their somatic and psychiatric health. Patients with missing data of criteria of the metabolic syndrome were excluded from the analysis. The metabolic syndrome was defined by the criteria of the National Cholesterol Education Program (NCEP) Expert Panel on Detection,

Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III).<sup>4</sup> Furthermore, we estimated the prevalence of the metabolic syndrome according to the definition of the ATP IIIa (adapted version of the ATP III)<sup>5</sup> and the International Diabetes Federation (IDF).<sup>6</sup> When a fasting assessment was not available, hyperglycemia was defined by HbA1c of more than 6.2% instead of glucose criterion of the ATP III/NCEP (ATP IIIa, IDF: HbA1c >5.7%) and hypertriglyceridemia by triglycerides of more than 2.2 mmol/L. We conducted a subanalysis to estimate the prevalence of the metabolic syndrome in the cohort of patients with a measure of fasting glucose. We used the Mann-Whitney test and the  $\chi^2$  test to compare the characteristics of the patients with

metabolic syndrome (ATP III/NCEP) to those without. A positive family history was defined as having diabetes or cardiovascular disease (including hypertension) in first line family members such as parents and siblings.

In total, 433 patients were included in the analysis. This was 55% of all patients (n = 785) treated in the department of psychotic disorders during the inclusion period. Age and sex distribution were similar between included patients and total population. Of the total population, 155 patients did not participate in the program and another 197 patients participated partly and were excluded because data was missing to calculate the metabolic syndrome. Of the included patients, 32% (n = 138) had metabolic syndrome according to the definition of NCEP/ATP

III, 36% (n = 158) according to the ATP IIIa definition, and 38% (n = 165) according to the IDF definition. In the group of patients (n = 150) with a measure of fasting glucose, 32% (n = 48) had metabolic syndrome according to the definition of NCEP/ATP III, 36% (n = 54) according to the ATP IIIa definition, and 40% (n = 60) according to the IDF definition. The most frequently fulfilled criterion (ATP III/NCEP definition) in all female patients was abdominal obesity (66%, n = 102) and in all male patients, hypertension (49%, n = 136). The criterion for hyperglycemia was least frequently fulfilled in male (10%, n = 27) and female patients (10%, n = 16). Patients with metabolic syndrome were significantly older, had a longer duration of disease, and significantly more

**TABLE 1.** Comparison of Patients With Metabolic Syndrome to Those Without Metabolic Syndrome

	Metabolic Syndrome, n = 138	No Metabolic Syndrome, n = 295	P
Sex (male)	65% (n = 90)	64% (n = 189)	0.816
Age, yr*	39 (30–49)	35 (26–45)	0.003
Duration of disease, yr*	10 (4–17); missing: n = 13	7 (2–15); missing: n = 30	0.008
Cardiovascular and metabolic risk factors			
Positive family history of cardiovascular diseases	17% (n = 24)	11% (n = 33)	0.075
Positive family history of diabetes	14% (n = 19)	6% (n = 19)	0.012
Smoking	68% (n = 94)	58% (n = 171)	0.043
Criteria of the metabolic syndrome			
Waist circumference in cm*			
Female, >88 cm†	110 (101–122)	90 (79–99)	0.000
Male, >102 cm†	108 (103–116)	91 (84–99)	0.000
Systolic blood pressure in mm Hg,* ≥130 mm Hg†	130 (120–140)	120 (110–130)	0.000
Diastolic blood pressure in mm Hg,* ≥85 mm Hg†	80 (80–90)	80 (70–80)	0.000
Triglycerides in mmol/L,* ≥1.7 mmol/L†,‡	2.2 (1.8–3.1)	1.2 (0.9–1.6)	0.000
HDL cholesterol in mmol/L*			
Female, ≤1.3 mmol/L†	1.1 (1.0–1.3)	1.6 (1.3–1.8)	0.000
Male, ≤1.0 mmol/L†	1.0 (0.8–1.0)	1.2 (1.1–1.5)	0.000
Fasting glucose in mmol/L,* ≥6.1 mmol/L†	5.4 (4.9–6.3); missing: n = 90	5.0 (4.7–5.3) missing: n = 193	0.000
HbA1c in %, * ≥6.2%†	5.7 (5.5–6.0)	5.4 (5.2–5.6) missing: n = 4	0.000
Diagnosis			
Schizophrenia	73% (n = 101)	62% (n = 183)	0.005 (df = 3)
Schizoaffective disorder	18% (n = 25)	15% (n = 44)	
Other psychotic disorder	7% (n = 9)	19% (n = 55)	
Other psychiatric diseases with psychotic symptoms	2% (n = 3)	4% (n = 13)	
Antipsychotic drug therapy			
No antipsychotic drugs	3% (n = 4)	12% (n = 34)	0.000 (df = 5)
Olanzapine (monotherapy)	17% (n = 23)	29% (n = 87)	
Clozapine (monotherapy)	25% (n = 34)	16% (n = 48)	
Risperidone (monotherapy)	18% (n = 25)	19% (n = 55)	
Other monotherapy	18% (n = 25)	12% (n = 34)	
Combinations of antipsychotic drugs	20% (n = 27)	13% (n = 37)	

\*Variables are presented as median (interquartile range).

†Cutoff levels for the criteria of the metabolic syndrome (ATP III/NCEP).

‡For nonfasting triglycerides, we used a cutoff of 2.2 mmol/L.

frequently, a positive family history of diabetes (Table 1). The diagnoses of schizophrenia and schizoaffective disorder were more prevalent in patients with metabolic syndrome than in patients without metabolic syndrome. Most patients with other psychotic disorders did not have metabolic syndrome. Seventy-six percent ( $n = 331$ ) of all patients received 1 antipsychotic drug; patients with metabolic syndrome received more often clozapine than olanzapine, whereas patients without metabolic syndrome received more often olanzapine than clozapine. Furthermore, patients with metabolic syndrome received more often a combination of antipsychotic drugs and less often no antipsychotic drug than those without metabolic syndrome.

## DISCUSSION

In our study, 32% of patients with psychotic disorders fulfilled the criteria for metabolic syndrome. This prevalence was lower than reported from studies conducted in patients with psychotic disorders in North America (United States: 41%,<sup>2</sup> Canada: 45%),<sup>7</sup> and at the high end compared to studies conducted in Europe (Spain: 25%,<sup>3</sup> Belgium: 28%,<sup>1</sup> and Sweden: 35%).<sup>8</sup> It was considerably higher than in the general Dutch population: in slightly older cohorts, it ranged from 10% to 12% for females and from 16% to 19% for males.<sup>9</sup>

The most concerning finding was the high prevalence of abdominal obesity in female patients. Even females without metabolic syndrome fulfilled on average the waist circumference criterion. Similar findings have been described previously and resulted in a higher prevalence of metabolic syndrome in females compared with males.<sup>2,3</sup> We found an equal prevalence of the metabolic syndrome in males and females; however, compared with the general population, the prevalence of metabolic syndrome in female psychotic patients was more elevated than in male patients. Similar to van Winkel et al,<sup>10</sup> we found the highest prevalence of metabolic syndrome in patients with schizoaffective disorders followed by those with schizophrenia. Patients with other psychotic disorders had the lowest prevalence of metabolic syndrome, but those also had the shortest mean duration of disease (data not shown).

Clozapine and olanzapine have a similar high risk of causing diabetes, dyslipidemia, and overweight.<sup>11</sup> In our study, patients with metabolic syndrome received more often clozapine than olanzapine, whereas those without metabolic syndrome received more often olanzapine

than clozapine. These differences might be due to the different switching strategies for these drugs. Patients with metabolic adverse effects may have been more easily switched to other drugs from olanzapine than from clozapine because clozapine was mostly prescribed for therapy-resistant patients, whereas olanzapine was a first-choice drug. This is supported by the younger age and shorter duration of disease of the patients receiving olanzapine compared with those receiving clozapine (data not shown). The prevalence of metabolic syndrome was also elevated in patients receiving more than 1 antipsychotic drug. Most probably, this is caused by other factors related to the use of combinations than the combination itself. Correll et al<sup>12</sup> demonstrated that antipsychotic polypharmacy was related with a higher prevalence of metabolic syndrome, however, not after correcting for age, diagnosis, treatment, and body mass index.

This study was limited by the use of HbA1c as a surrogate parameter for fasting glucose. However, when only including patients with fasting glucose measures in the analysis, we found equal or similar prevalences of the metabolic syndrome. In conclusion, our study described that the prevalence of metabolic syndrome among patients with psychotic disorders in the Netherlands is high and screening and treatment are strongly required.

## AUTHOR DISCLOSURE INFORMATION

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## Valproic Acid–Induced Myopathy in a Patient With Schizoaffective Disorder

### To the Editors:

Anticonvulsant valproic acid (VPA) has found increasing use as a psychotropic agent in the treatment of manic episodes associated with bipolar disorder. Its common adverse effects, for example, nausea, vomiting, weight gain, somnolence, hyperammonemia, and tremor, are well known. However, with an expanding number of indications and VPA-exposed patients, rare and potentially life-threatening adverse effects emerge.

Particularly, in geriatric psychiatry dealing with patients with multimorbidity, polypharmacy and drug interactions are a common problem. Therefore, the service of a routine clinical-pharmacological medication review is an important tool to recognize and prevent adverse drug events.

To our knowledge, we here report the first case of myopathy associated with valproic acid in an elderly patient affected by schizo-affective disorder.

### CASE REPORT

A 85-year-old female patient with a history of schizo-affective disorder and dementia was admitted to a hospital because of a manic episode. She was further affected by hypothyroidism and hypertension. Her medications on admission were quetiapine (200 mg/d), nifedipine (10 mg/d), torsemide (10 mg/d), levodopa (75 µg/d), and acetylsalicylic acid

(100 mg/d) for secondary prevention after stroke. Valproic acid was initiated 4 days after hospitalization and titrated to a dosage of 300 mg twice daily.

On the fourth day after starting with VPA, she complained about muscle pain and weakness. Laboratory evaluation revealed a 5-fold increase in myoglobin level (292 µg/L; Fig. 1), a 6-fold increase in creatine kinase (CK) level (14.4 µmol/L), and slightly increased liver enzyme concentrations (alanine aminotransferase level, 0.72 µmol/L and aspartate aminotransferase level, 0.93 µmol/L). In addition, the creatinine level was increased to 112 µmol/L. Further blood parameters and temperature were within the reference range. Serum concentration of VPA was therapeutic with 46 µg/mL (range, 30–100 µg/mL). The relatively low quetiapine dose resulted in a blood concentration (25 ng/mL) below the therapeutic range (70–170 ng/mL).

During the routine clinical pharmacological ward round, the case was discussed, and discontinuation of VPA and quetiapine was decided. Long-acting torsemide was replaced by furosemide (10 mg/d). Pipamperone was started.

The maximum myoglobin and CK levels (myoglobin, 345 µg/L; CK, 17.8 µmol/L) were detected 6 days after stopping VPA and quetiapine. Obviously, the half-life of VPA was increased; we calculated it and determined a prolonged half-life of VPA up to 30 hours (normal, 9–16 hours; Kinetica version 4.4 [Thermo Electron Corporation, Waltham, Mass]).

A reason for this prolongation could be a drug interaction with the newly administered neuroleptic pipamperone, resulting in a reduced VPA clearance.

Fifteen days after cessation of VPA and quetiapine, myoglobin and CK levels returned to normal. Even reintroduction of quetiapine to a maintenance dosage of 450 mg/d and the continuous administration of 40 mg of pipamperone 3 times per day caused no deterioration of muscle symptoms and laboratory parameters.

Psychiatric medication and the course of myoglobin and VPA concentrations are shown in Figure 1.

Myolysis commonly occurs in response to seizures, trauma, hyperthermia, or infections.<sup>1</sup> We supposed VPA to be the culprit agent based on the following: there is a temporal relationship between the onset of symptoms, which occurred shortly after introduction of the drug, and the clinical resolution, which followed upon discontinuation of the drug. Moreover, the half-life of VPA obviously was prolonged. In addition, there was no alternative explanation for the myopathy, as the patient had no history of seizure and no signs of trauma, hyperthermia, or infection and, except quetiapine, no drugs, which are known to cause myopathy such as statins.

Although rare, a few other case descriptions to support our hypothesis were found. The occurrence of acute rhabdomyolysis triggered by valproic acid was reported in a patient with carnitine palmitoyltransferase type II deficiency.<sup>2</sup> Furthermore, cases of VPA-induced

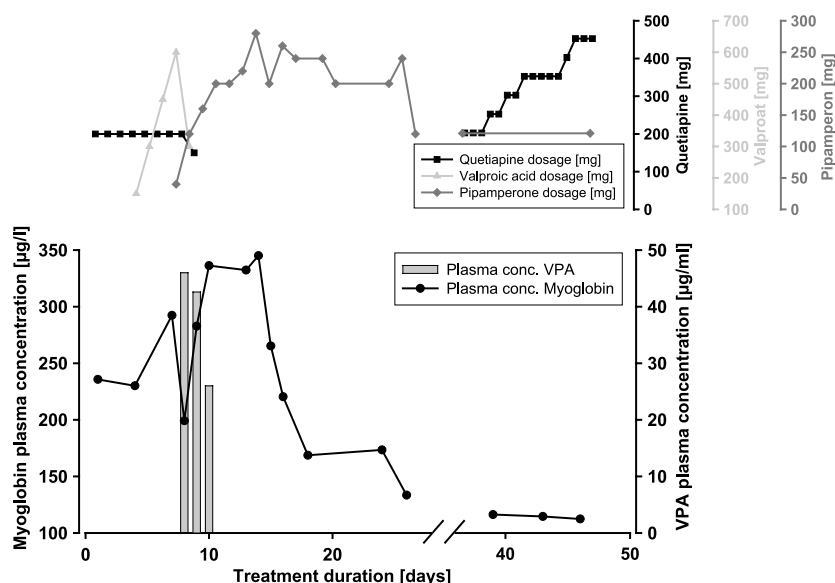


FIGURE 1. Psychiatric medication and course of myoglobin concentration.

myopathy in children were described in the literature.<sup>3–5</sup>

The mechanism of this adverse effect is unknown. A reasonable explanation could be the inhibition of the mitochondrial  $\beta$ -oxidation by valproic acid and its metabolite 2-*n*-propyl-4-pentenoic acid. This has been shown in rat liver and could also lead to impairment of  $\beta$ -oxidation in muscle tissue.<sup>6</sup>

With regard to quetiapine, several case reports describing rhabdomyolysis or a massive increase in serum CK associated with quetiapine therapy or overdose were taken into consideration.<sup>7–10</sup> In the present case, the quetiapine plasma level was subtherapeutic at the onset of symptoms. Moreover, after readministration, myoglobin and CK levels remained normal.

Admittedly, Meltzer et al<sup>11</sup> described a few cases with other atypical antipsychotics in which increased serum CK activity decreased to normal despite continued treatment. Therefore, quetiapine and a pharmacodynamic drug interaction between quetiapine and VPA cannot completely be excluded as cause for the described adverse drug reaction.

Overall, using known probability assessment scores, a possible adverse drug reaction had occurred.<sup>12,13</sup>

In conclusion, psychiatrists should be aware of VPA causing myopathy apart from atypical antipsychotic drugs in older people. Furthermore, cooperation with clinical pharmacologists is a helpful tool to recognize and manage adverse drug events.

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### Allopregnanolone Levels Before and After Selective Serotonin Reuptake Inhibitor Treatment of Premenstrual Symptoms

#### To the Editors:

Severe premenstrual syndrome (PMS) is characterized by disabling physical and

psychological symptoms that occur during the luteal phase of the menstrual cycle. Allopregnanolone has been implicated in the pathophysiology of mood disorders, stress, and possibly PMS and premenstrual dysphoric disorder.<sup>1</sup> There is some evidence that response to treatment of PMS correlates with decreased allo levels.<sup>2</sup> We previously found in a small pilot study that women with PMS who improved with selective serotonin reuptake inhibitor (SSRI) treatment had significantly lower allo levels at treatment end point than the unimproved subjects.<sup>3</sup> However, a major limitation of that study was that pretreatment allo levels were not evaluated, and associations between SSRI treatment and changes in allo could not be determined. The aims of the present study were to identify changes in allo levels after SSRI treatment and determine whether the changes in allo levels were related to improvement in PMS symptoms. Based on our previous pilot study, we hypothesized that high allo levels decreased with SSRI treatment and that the changes were associated with symptom improvement. We also hypothesized that low allo levels at baseline increased, as previously shown in patients with depression, and that the changes were associated with improvement of dysphoric symptoms.<sup>4</sup>

This was a prospective study of 46 women with PMS, whose conditions were diagnosed with clearly defined criteria including daily symptom ratings and treated with sertraline as described elsewhere.<sup>5</sup> All participants who had serum samples collected within 8 days before menses both before and after sertraline treatment and met the criteria for this study were included. Inclusion criteria included regular menstrual cycles in reference range, a positive result for urine test indicating probable ovulation, and general good health. Exclusions included any hormone use, other treatments for PMS, any major Axis I psychiatric diagnosis currently or in the past year, lifetime diagnosis of bipolar disorder or psychosis, and alcohol or drug abuse. Flexible regimens were used; all but 4 subjects had luteal phase dosing (14 days before estimated menses through 2 days after the onset of menses) with sertraline dosages of 50 or 100 mg/d. All subjects signed consent forms approved by the university institutional review board.

Serum samples were collected at approximately day  $4 \pm 3$  days before menses in an untreated screen cycle and after 2 to 3 months of SSRI treatment. The cycle day was confirmed by the date of menses after each blood draw using backward count from the first day of menses. The samples

**TABLE 1.** Unadjusted Association Between Baseline Allopregnanolone Levels and Symptom Improvement

Variable*	Baseline Allo Low Group	Baseline Allo Mid Group	Baseline Allo High Group	P
Hopelessness	6.77 (3.81–9.74)	6.62 (3.45–9.79)	2.03 (–1.03 to 5.09)	0.051
Out of control	7.37 (4.14–10.62)	10.25 (6.78–13.72)	2.2 (–1.14 to 5.56)	0.004
Decreased social activity	6.69 (3.4–9.95)	6.12 (2.63–9.61)	1.83 (–1.54 to 5.20)	0.091
Depression	9.23 (6.52–11.92)	8.51 (5.62–11.4)	3.59 (0.789 to 6.33)	0.009

\*Values are the mean absolute change in the DSR symptom score with 95% confidence interval.

were stored at  $-80^{\circ}\text{C}$  and measured in the laboratory of Dr Cheryl Frye according to previously established methods.<sup>6</sup> The minimum detectable limit of the assay was 100 pg. The intra-assay and interassay coefficients of variance were 0.12 and 0.15, respectively.

Premenstrual syndrome symptoms were rated daily by the participants, and scores were obtained in the same menstrual cycles as the allo measures. The validated daily symptom report (DSR) included 17 mood, behavioral, and physical symptoms of PMS that were rated on a 5-point scale ranging from 0 (not present) to 4 (very severe).<sup>7</sup> Premenstrual symptom scores were obtained by summing the daily ratings for the last 6 days of each menstrual cycle.

General linear regression models were used to examine the associations between baseline and end point measures. Baseline allo was examined as a continuous variable and also as a class variable divided into tertiles and in 2 groups to examine the a priori hypothesized changes for high and low baseline allo levels. Results were consistent. Multivariable linear regression models were adjusted for cycle day and for a history of depression as a potential confounder. Changes in premenstrual symptoms were compared between the 3 baseline allo groups. *F*, Student *t*, and  $\chi^2$  or Fisher exact tests were used as appropriate for the data, with 2-tailed  $P < 0.05$  considered statistically significant. The SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses. Post hoc power calculations were performed and indicated 81% power for aim 1 but only 43% power to detect a significant improvement in symptoms compared between baseline allo groups.

The mean (SD) age of the 46 participants was 31.1 (7.0) years. The mean cycle day before menses was  $-3.70$  (2.74) at the pretreatment baseline and  $-3.52$  (SD 2.21) at treatment end point. The mean allo level was 2.55 (1.22) ng/mL at baseline and 2.46 (SD 1.06) ng/mL at treatment end point.

Thirty-nine percent of the subjects (18/46) had a history of depression.

The change in allo after sertraline treatment was significantly associated with baseline allo levels in a linear regression model adjusted for cycle day ( $P < 0.0001$ ). We examined the same models with baseline allo levels divided into tertiles as hypothesized. Allo levels significantly decreased in the high baseline allo group ( $P < 0.001$ ) and significantly increased in the low baseline allo group ( $P = 0.026$ ) compared with the baseline mid allo group. Allo levels did not change significantly in the mid group ( $P = 0.652$ ). We repeated these analyses with baseline allo levels divided at the median (2.24 ng/mL) with consistent results: allo levels significantly increased in the low baseline allo group compared with the high baseline allo group ( $P < 0.0001$ ). There was no difference in allo levels compared between women with and without a history of depression, either at baseline ( $P = 0.72$ ) or after sertraline treatment ( $P = 0.30$ ).

Sixty-three percent of the subjects (29/46) improved with SSRI treatment as defined by 50% improvement or more in the total premenstrual DSR score at end point compared with baseline. We examined the association of baseline allo levels with the change in 7 selected DSR symptoms that were hypothesized a priori to be associated with allo levels. Improvements in feeling out of control ( $P = 0.004$ ), depression ( $P = 0.022$ ), and hopelessness ( $P = 0.051$ ) were associated with baseline allo. For each of these symptoms, the baseline low and mid allo groups improved, whereas those with high baseline levels had little change in symptoms (Table 1). There was no significant association between baseline allo groups and improvement of the total DSR score ( $P = 0.391$ ).

## DISCUSSION

In this investigation, the subjects with low baseline allo levels had a significant

rise in allo after SSRI treatment, whereas those with high baseline allo levels had significant decreases in allo. Although these changes may simply reflect regression to the mean, other interpretations can be considered. In studies of patients with depression, low allo levels were associated with depressive symptoms; the allo levels increased and depressive symptoms decreased with fluoxetine treatment,<sup>4</sup> suggesting that a dysregulation of progesterone metabolism may be corrected with an SSRI.<sup>8</sup> Other studies found that both high and low levels of allo had negative associations with mood in postmenopausal women treated with progesterone, suggesting a bimodal association between allo and mood.<sup>9</sup> Monteleone et al<sup>10</sup> reported that patients with PMS had significantly lower luteal phase levels of allo compared with normal controls and a reduced response to a gonadotropin-releasing hormone test, suggesting that impairment of a  $\gamma$ -aminobutyric acid-mediated anxiolytic effect led to the reduced sense of well-being in the luteal phase. In contrast, other studies indicated that high allo concentrations were associated with premenstrual dysphoric (PMDD) and panic disorders.<sup>11,12</sup> It is also possible that the fluctuations of allo, that is, the long-term exposure and withdrawal of the neurosteroid over the menstrual cycle, result in anxiogenic effects.<sup>13</sup>

Baseline allo levels were significantly associated with differential improvement in specific and primarily dysphoric symptoms. However, neither levels nor changes of allo were associated with total premenstrual symptom scores. Although noting that the power to detect associations between changes in allo and symptom reduction was low in this pilot study (43%), existing data suggest that allo may not be associated with all symptoms that are included in the highly heterogeneous definition of the syndrome.

Further studies to assess fluctuations of allo over time before and after sertraline therapy may be informative. The study did not include a placebo-treated group, and comparisons of allo changes between drug- and placebo-treated groups are needed to support or refute these findings. These pilot data did not allow further investigation of the dosing duration and diagnostic differences (PMS vs PMDD), which may be valuable to study in the future. Single luteal measures are difficult to interpret with confidence given the variability in luteal phase allo levels, and daily luteal measures might improve precision in further studies. Inclusion of follicular and ovulatory hormone levels would also provide a more complete



investigation of the associations between allo and PMS symptoms.

Overall, the data suggest that allo levels differ in subjects with a different complement of symptoms and that the effect of an SSRI depends on both the specific symptoms and the endogenous allo levels. Further clarification of the role of allopregnanolone in PMS may contribute to understanding the pathophysiology of the syndrome and to predicting which women will respond to treatment with current medications such as SSRIs. If allo is ultimately found to be important in the etiology of PMS or PMDD, novel treatments targeting allo or other GABAergic targets might be developed.

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## Influence of Antidepressant Use on Glycemic Control in Patients With Diabetes Mellitus An Open-Label Comparative Study

#### To the Editors:

Depression is a common comorbidity in patients with diabetes mellitus<sup>1</sup> and is frequently treated with antidepressants. Depression in diabetic patients is associated with poor glycemic control,<sup>2</sup> which in turn is a risk factor for microvascular and macrovascular complications. Antidepressants, however, may also interfere with glucose homeostasis and thereby further complicate glycemic control. It has been postulated that the interference of antidepressants on glucose homeostasis is bidirectional depending on the complex pharmacology of antidepressants. An increase in norepinephrine function and a blockade of the histamine H<sub>1</sub> and 5-HT<sub>2C</sub> receptors seem to increase glucose levels because of reducing both insulin release and insulin sensitivity. In contrast, an increase in serotonergic function seems to increase insulin sensitivity and reduce glucose levels.<sup>3</sup> This implies that those antidepressants that inhibit the serotonin reuptake transporter may have insulin-sparing effects and could be advantageous for patients with diabetes mellitus treated for comorbid depression. However, evidence on this subject is still limited. In this open-label comparative study, we evaluate the change in insulin requirements of 4 patients starting with a serotonergic antidepressant compared with 8 diabetic patients not using any antidepressant.

The source population consisted of patients attending the diabetes outpatient clinic of the Orbis Medical Center. The Orbis Medical Center is a 700-bed teaching hospital serving more than 180,000 patients in the south of the Netherlands. The diabetes outpatient clinic is visited by patients with new-onset diabetes and by diabetic patients who need additional care. Patients visit the outpatient clinic on a 3-monthly regular basis. Advice is given regarding (1) insulin injection regimen based on glucose self-monitoring (combined with oral antidiabetics), (2) handling diabetic complications, and (3) lifestyle such as dietary advice. Some patients register their glucose measurements and the amount of injected insulin regularly in a diabetes diary. For all patients, the current amount of injected insulin and changes in the amount of injected insulin are also recorded by the diabetic nurse in the



TABLE 1. Description of the Users and Nonusers

Patient	Antidepressant	Age, yr	Sex	BMI, kg/m <sup>2</sup>	Increase in Eating, $t = -180$ to 0	Diabetes Type	Duration of Diabetes, yr	SDS Score*	Oral Antidiabetics	Hyperglycemia-Inducing Comedication	Hypoglycemia-Inducing Comedication	Insulin Dose, $t = -30$ to 180 IU/d	$\Delta\%$ Insulin Before Index Date, $t = -30$ to 180	$\Delta\%$ HbA <sub>1c</sub> Before Index Date, $t = -30$ to 180
User 1	Citalopram	72	Female	24	No	1	8	44	None	None	Yes	42	14.3	-17.2
User 2	Sertraline	67	Female	33	No	2	11	42	None	Yes	Yes	120	0.0	0.0
User 3	Sertraline	37	Male	28	No	2	3	53	None	Yes	Yes	123	4.1	-15.1
User 4	Paroxetine	76	Female	21	No	1	5	27	None	Yes	None	34	-8.8	3.4
Means		62.9		26.5				41.5				79.8	2.4	-7.2
Nonuser 1	None	53	Male	38	No	2	11	41	Metformin	Yes	Yes	162	6.2	21.8
Nonuser 2	None	74	Male	35	No	2	3	46	None	Yes	Yes	72	19.4	7.7
Nonuser 3	None	52	Male	30	No	2	12	38	Metformin	Yes	Yes	59	86.4	-15.6
Nonuser 4	None	72	Female	31	No	1	16	38	None	None	Yes	74	13.5	7.0
Nonuser 5	None	54	Male	23	No	1	8	27	None	None	None	36	0.0	-5.9
Nonuser 6	None	72	Male	31	No	2	25	50	Metformin	None	Yes	58	10.3	4.7
Nonuser 7	None	75	Male	35	No	2	5	32	Metformin	Yes	Yes	134	4.5	-14.3
Nonuser 8	None	65	Male	24	No	1	35	27	None	Yes	Yes	53	5.7	-1.4
Means		64.6		30.9				37.4				81.0	18.3	-0.5

$P > 0.05$  for differences between means of users and means of nonusers for: age, BMI, SDS score, insulin dose  $t = -30$  to 180, HbA<sub>1c</sub> before index date, and  $\Delta\%$  HbA<sub>1c</sub>.  
 \*SDS score: lower than 50, within reference range; 50 to 59, minimal to mild depression; 60 to 69, moderate to severe depression; higher than 70, severe depression.

electronic patient record. Laboratory data are collected in the same record.

Patients were included if they met the following inclusion criteria: (1) they started with a serotonergic antidepressant (index date), (2) used this antidepressant for at least 180 days, (3) had no prescription for any antidepressant for 180 days before the index date (wash-out period), (4) were 18 years or older at the index date, and (5) used insulin for at least 30 days before the index date. Patients were followed up for 210 days. Serotonergic antidepressants were defined according to a model classifying antidepressants based on their binding properties to the most common transporter and receptor sites. Serotonergic antidepressants included citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine.<sup>4</sup> To study the natural course of insulin requirements during the study period, we randomly selected 2 nonusers of antidepressants for each user. The index date for nonusers was defined as the inclusion date, and nonusers were included if they met the following inclusion criteria: (1) they were 18 years or older at the index date, (2) used insulin for at least 30 days before the index date, and (3) did not use any antidepressant at inclusion or during the follow-up period of 210 days.

The primary outcome of this study was the mean relative difference of insulin requirements over time (at 0, 30, 60, 120, and 180 days after the index date). The mean insulin requirement at 30 days before the index date was taken as the reference value. Insulin requirements at different time points were obtained from diabetes diaries and/or from the electronic patient record. We also collected the most recent available HbA<sub>1c</sub> values before the index date and between 90 and 180 days after the index date.

The following covariates were obtained to present individual differences between subjects: age, sex, body mass index (BMI), changes in eating behavior for a period of 180 days before the index date, diabetes type, duration of diabetes, use of oral antidiabetics, current use of potentially hypoglycemia- and hyperglycemia-inducing medications, and depression score at the index date. Current use of antidiabetic medication and use of hyperglycemia- or hypoglycemia-inducing comedication were defined as use of such medication at the index date. Hyperglycemia- and hypoglycemia-inducing comedications were identified by a literature search.<sup>5</sup> The Self-Rating Depression Scale (SDS) from Zung was used as a measure for depression.

The prevalence of each characteristic was determined at index date. The non-parametric Mann-Whitney *U* test was used to compare changes in mean insulin dose and HbA<sub>1c</sub> at different time points between users and nonusers.

Four serotonergic antidepressant users and 8 nonusers were included from April 2007 to March 2008. Table 1 provides a description of the individual users and nonusers. The mean insulin dosage 30 days before index date was 79.8 IU/d for the users and 81.0 IU/d for the nonusers ( $P = 0.68$ ). The mean insulin dose increase in the period from 30 days before the index date to 180 days after the index date was 2.4% for the users and 18.3% for the nonusers ( $P = 0.15$ ). Nonuser 3 showed the biggest insulin dose increase in this period (86.4%). Excluding nonuser 3 from the analysis, the mean insulin dose increase in the nonusers in the period from 30 days before index date to 180 days after the index date was 8.5%. The standardized mean insulin doses did not reach statistical difference between users and nonusers at any time during follow-up.

HbA<sub>1c</sub> levels at index date were 8.1% for the users and 7.6% for the nonusers ( $P = 0.81$ ). The mean relative decrease of HbA<sub>1c</sub> levels during follow-up was 7.2% for the users and 0.5% for the nonusers ( $P = 0.37$ ).

## DISCUSSION

Insulin requirements in patients starting with a serotonergic agent increased 2.4% during follow-up compared with 18.3% in the nonusers. The HbA<sub>1c</sub> levels decreased in users of serotonergic agents compared with nonusers. However, these differences were not statistically significant.

A limitation to this open-label comparative study is that it was underpowered for statistical significance as is illustrated by the fact that a single patient was responsible for an important increase in mean insulin requirements in the nonuser group. However, evidence from earlier studies with other outcome parameters showed the same patterns as we have found. In patients with type 2 diabetes mellitus and in nondiabetic patients, the use of fluoxetine and the serotonergic anorectic agent fenfluramine increased insulin sensitivity in the short term.<sup>6,7</sup> In a recent longitudinal follow-up database study of patients with types 1 and 2 diabetes mellitus, users of selective serotonergic reuptake inhibitors (SSRIs) showed a 13% decrease in insulin requirements during SSRI use, whereas no change was found in users of tricyclic antidepressants and nonusers.<sup>8</sup>

We analyzed types 1 and 2 diabetic patients together and did not stratify according to diabetes type. If SSRIs improve insulin sensitivity, you should not expect improvement in type 1 diabetic patients because insulin sensitivity is not impaired in this group of patients. However, previous evidence in healthy subjects and subjects with type 1 diabetes mellitus revealed that the use of antidepressants increased insulin sensitivity and may even cause hypoglycemia.<sup>9,10</sup> Because it has been documented that SSRI antidepressants may improve insulin sensitivity in both types of diabetes, we feel that it is justified to include both types of diabetic patients in our study and to pool the results.

An interesting question is whether the insulin-sparing effects we have found are caused by a pharmacological effect of serotonergic agents or by a change in the course of depression. There are several arguments against the assumption that the course of the depression has influenced our study outcomes. First, patients recovering from a depression are more likely to have an increased food intake resulting in increased insulin requirements. We have found the opposite effect. Second, referring to the SDS scores the patients in our study population were not clinically depressed. Third, just before the index date, users and nonusers showed similar insulin requirements (although there was not enough power to detect any dissimilarity). Fourth, questions about changes in eating behavior 180 days before the index date did not reveal any differences between the users and nonusers.

In conclusion, the question whether antidepressants have insulin-sparing effects remains unsolved at this stage. However, the results of this open-label comparative study show the same patterns as other studies: serotonergic agents may increase insulin sensitivity, lower glucose levels, decrease HbA<sub>1c</sub>, and decrease insulin requirements. Therefore, treating a depressed diabetic patient with a serotonergic agent combined with an accurate glucose self-monitoring seems a good option. Additional research with more patients is needed to confirm these results and to establish the clinical relevance of these findings.

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## AUTHOR DISCLOSURE INFORMATION

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## Hallucinations Associated With Modafinil Treatment for Narcolepsy

### To the Editors:

Modafinil is a wake-promoting agent that is pharmacologically different from other stimulants.<sup>1,2</sup> It has been investigated in healthy volunteers, as well as in individuals with clinical disorders associated with excessive sleepiness, fatigue, impaired cognition, and other symptoms.<sup>1,2</sup> In sleep-deprived individuals, modafinil improves mood, fatigue, sleepiness, and cognition to a similar extent as caffeine, but has a longer duration of action.<sup>1,2</sup> Evidence for improved cognition in non-sleep-deprived healthy volunteers is controversial.<sup>1,2</sup> Modafinil has been approved by the US Food and Drug Administration for the treatment of 3 disorders. It improves excessive sleepiness and decreases illness severity in narcolepsy, shift work sleep disorder, and sleep apnea with excessive sleepiness despite optimal continuous positive airway pressure therapy. However, its impact with respect to workplace safety and on the morbidities associated with these disorders has not been determined. Here, we report a case of psychotic symptoms induced by modafinil treatment.

Our patient was a 25-year-old woman with a 10-year history of narcolepsy. Her

main symptoms were excessive daytime sleepiness and severe sleep paralysis. Neither cataplexy nor hypnagogic hallucinations were observed. She had been treated with methylphenidate for 5 years in a previous sleep clinic. However, because of insufficient improvement of her symptoms, she moved back to her hometown for treatment of her narcolepsy. To alleviate her symptoms, modafinil was administered and titrated up to 300 mg/d in our hospital. The patient's symptoms improved markedly and her Epworth Sleepiness Scale score dropped from 17 to 6 points. However, she did experience dry mouth and tachycardia while on therapy from day 1 to day 5. After 5 days, she continued on 300-mg modafinil per day without any side effects. Approximately 6 months after the initiation of modafinil therapy, she reported seeing white smoke coming from her computer. She also reported an experience where she felt like a few people were behind her and she heard them talking when there was no one else present. These symptoms appeared 12–24 hours after modafinil administration. Because of her visual and auditory hallucinations, and delusions of reference, modafinil therapy was discontinued and these psychotic symptoms disappeared. However, because her narcoleptic symptoms reappeared, modafinil dosing was restarted every other day. Although hallucinations occasionally recurred, she learned to cope with them through psycho-education.

There have been five case reports of psychosis associated with modafinil administration.<sup>3–7</sup> Among these, modafinil was used for the treatment of narcolepsy in two cases.<sup>4,7</sup> One described a 17-year-old man who developed persecutory and referential delusions in addition to auditory and visual hallucinations while taking 400 mg modafinil per day.<sup>4</sup> Prior to the onset of symptoms, he had tolerated the same dose for a year without ill effect. This case was quite similar to ours. The other narcolepsy related case involved a 31-year-old woman who developed temporary persecutory delusions and auditory hallucinations after taking an overdose of 500 mg modafinil and 300 mg of caffeine.<sup>7</sup> The other 3 cases included a schizophrenic patient, 3 a research volunteer, 5 and a patient with a mood disorder and substance abuse.<sup>6</sup>

Although the precise mechanism of modafinil is not known, the waking effects of modafinil are thought to be mediated by activation of noradrenergic  $\alpha$  1 receptors based on several animal studies.<sup>1,2</sup> In addition, haloperidol did not block the behavioral effect of modafinil in animals,

although it had blocked the behavioral effects of amphetamine. This suggests that modafinil has a different mechanism of action compared to other stimulants.<sup>8</sup> Recent animal studies have demonstrated that modafinil enhances the extracellular levels of dopamine promoting wakefulness. It has also been associated with dopamine release from striatal neurons.<sup>9,10</sup> These dopaminergic effects may be related to the psychotic symptoms induced by modafinil treatment.

Our case report suggests that long-term administration of modafinil may induce psychotic symptoms, as have other stimulants such as amphetamines. Although rare, the potential for psychotic symptoms when using modafinil therapy should be kept in mind.

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**Response to Shen J, Kobak K, Zhao Y, et al. Use of Remote Centralized Raters Via Live 2-Way Video in a Multicenter Clinical Trial for Schizophrenia. (*J Clin Psychopharmacol.* 2008;28:691–693)**

**To the Editors:**

We applaud Shen et al<sup>1</sup> for their efforts to explore new methods that might enhance the ability of studies to successfully detect drug signals. The work is important because, for reasons that are not fully elucidated, a steadily increasing placebo response and decreasing drug response in schizophrenia trials have been noted over time, serving to potentially jeopardize signal detection of new agents.<sup>2</sup> In our view, the critical, unanswered question raised by the work<sup>1</sup> is whether the use of centralized raters represents an improvement over current practice with respect to solving the problems noted. The article<sup>1</sup> might have been more informative in this respect if it had described a comparison to site-based ratings in the same study as a control group. It would also be helpful to have more information on the severity and character of the psychotic symptoms in the report<sup>1</sup> because these symptoms could affect patients' cooperativeness with the central ratings procedures.

Current practice is to use trained investigators as site raters. We know that these raters have the capacity to make valid and reliable assessments of the mental state of patients. To date, site as opposed to centralized raters' ability to separate drug from placebo has supported the approval of every antipsychotic agent and, in fact, every commercially available central nervous system drug. In a recent review, Kemp et al<sup>2</sup> reported the diminution of drug-placebo differ-

ences when compared with earlier trials. Many potential explanations have been put forth, from overall changes in subject characteristics and motivation, to increasingly high clinician expectations about antipsychotic efficacy, to actual changes in studied drug efficacy. Unfortunately, although we know there is a problem, there is no clear answer as to how it can best be solved.

Advocating for a centralized ratings approach in the absence of data that it is superior to site-based ratings seems to be premature and potentially ill-advised. It may be the case that studies fare worse with central raters than they do with site raters who are able to perform in-person interviews. We have no information either way. Yet studies can easily be designed that compare same-patient ratings by site raters with those of centralized raters. Such studies, if done carefully, could afford the field a useful starting point to evaluate the potential benefits of centralized ratings with respect to placebo response, drug response, and, ultimately, signal detection.

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**Reply to Comments by Grunze et al**

**To the Editors:**

We agree with Dr Grunze et al on the need for empirical data on the relative efficacy of site versus central raters in both patient inclusion and outcomes assessment. It is because of this that Med-Avante has collaborated with several sponsors in conducting multiple head-to-head comparisons of site and central raters. The report by Shen et al<sup>1</sup> is one of the first publications from these efforts and describes only the central raters' outcomes as a way of addressing the feasibility (as noted by Grunze et al, not the superiority) of the methodology. It does clearly demonstrate both the technical feasibility of the video-conferencing methodology and the ability to assess patients with psychosis with this method.

We applaud these sponsors because research addressing methodological issues usually requires modifications of the study design that are not directly related to assessing drug efficacy or safety and may require additional costs. However, to adequately answer methodological questions, sponsors must be willing to share all data that will shed light on these questions. This may involve releasing data that are usually considered proprietary because it may be difficult to disentangle the issue of evaluating assessment methodology from examining efficacy/safety of the compounds being studied. As to the level of severity of the patients in the trial, the inclusion criteria required that the subjects be inpatients who were hospitalized owing to the acute exacerbation of their schizophrenia.<sup>2</sup>

Although there are as yet no published data on the relative efficacy of site versus central raters on signal detection, there are empirical data on the individual components of central ratings and increased signal detection. These have been reviewed elsewhere<sup>3</sup> and include larger signal detection with ratings of better quality, higher reliability, and improved blinding.

Finally, although the authors correctly state that site raters have been used



to support the approval of virtually every central nervous system drug to date, this does not necessarily mean it is the best process to achieve the ends of accurate assessment of drug efficacy or safety. Forty years ago, virtually all manuscripts were created on typewriters, but the advent of computerized word processing provided a far better methodology in virtually all respects. There is enormous concern about the increasing number of failed trials and the lack of precision in patient selection and outcomes assessment that might contribute to that phenomenon. We welcome the opportunity to further research the merits of this approach and to let all of the empirical data guide us in evaluating its relative merit.

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## Clinical Antipsychotic Trials of Intervention Effectiveness Study A Pragmatic Trial?

### To the Editors:

The recent increase in government sponsored pragmatic clinical trials in psychiatry has opened a new vista in un-

derstanding the effectiveness of drugs in a real world situation or on real world patients that are characteristic of those seen in daily clinical practice. However, industry-sponsored clinical trials are mainly intended to pass regulatory authorities and assess efficacy rather than effectiveness in a narrowly defined patient population in somewhat laboratory-controlled conditions.

The famous Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, funded by the National Institute of Mental Health,<sup>1</sup> was carried out to compare effectiveness and tolerability of atypical and typical antipsychotics in treatment of schizophrenia. One thousand four hundred sixty patients with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* schizophrenia were included, and those with first-episode/treatment-resistant schizophrenia were excluded. Patients with concomitant medications, medical illnesses, and/or substance abuse disorders were however included (in contrast to many other clinical trials conducted for regulatory purposes).

The dosing and dose equivalence used in the CATIE study<sup>2</sup> were somewhat different from American Psychiatric Association guidelines<sup>3</sup> especially for risperidone and ziprasidone. Clinical Antipsychotic Trials of Intervention Effectiveness investigators explain this difference by stating that “the average prescribed doses of these drugs in United States in patients with schizophrenia during the period in which the study was conducted (14 mg olanzapine/day, 3.8 mg risperidone/day, 388 mg quetiapine/day, and 125 mg ziprasidone/day) were generally similar to the ones we used.”<sup>4</sup> However, the mean modal doses in CATIE were, in fact, approximately 40% higher for olanzapine and quetiapine and 3% for risperidone, whereas 11% lower for ziprasidone,<sup>5</sup> making this an important issue to be addressed before trial completion.

Interestingly, this meant making certain assumptions about the dosage—where dosage of olanzapine used (30 mg) was much higher than what most practitioners prescribe; that of risperidone (6 mg) was well below the upper range of clinical use.<sup>6</sup> Yet, fewer than half of patients participating in the first phase received the maximum dose allowed of their assigned medication; however, rates of discontinuation owing to intolerability ranged from 10% to 19%. This raises an important query as to whether the 15% to 28% of patients who discontinued because of lack of efficacy received the maximum allowable dose.<sup>5</sup>

Another interesting thing to ponder over is why was the dosage of antipsy-

chotics restricted to that used in the CATIE trial? We feel that the choice of drug and its dosage (either typical or atypical antipsychotics) in the study design was carefully selected to avoid development of extrapyramidal adverse effects (EPAs) and tardive dyskinesia (TD), as these could have led to a sharp increase in dropout rates. Although the drugs used were Food and Drug Administration approved, the dosages of risperidone, ziprasidone, and perphenazine were kept at lower levels despite American Psychiatric Association recommendations.<sup>3</sup> Risperidone is also more likely to cause EPA and act like a typical antipsychotic<sup>7</sup> in dosages of more than 6 mg/d. Perphenazine was selected and used in modest dose for obvious reasons, as it causes less EPA and acts more like a second-generation than a first-generation antipsychotic such as haloperidol or chlorpromazine.<sup>6</sup>

The CATIE study observed that olanzapine (64%) was most effective for discontinuation rates, and efficacy of the conventional antipsychotic agent perphenazine seemed similar to that of quetiapine, risperidone, and ziprasidone (74%–82%). Neither were there higher rates of EPA noted on the Simpson-Angus Scale.<sup>6</sup> The rates of discontinuation because of intolerability ( $n = 213$  [15%]) were also statistically similar among the treatment groups. All this makes us wonder about the differences observed, if there was any.

Coming to the adverse effects, the CATIE study noted a high prevalence of metabolic syndrome (MS) in study participants (42%), with 51.6% of women and 36% of men developing MS during course of the study. These numbers are not surprising considering that most participants were already on prior treatment. Yet, these rates are much higher than the National Health and Nutrition Examination Survey (NHANES) trials<sup>8</sup> in both men (CATIE vs NHANES: 36% vs 19.7%) and women (51.6% vs 25%). The reported MS rates of CATIE is also higher than NHANES study, CLAMORS study (24.6%),<sup>9</sup> Finland study (19%),<sup>10</sup> and what we have reported earlier (10%).<sup>11</sup> Whether these differences in results are because of genetic or dosage variations between the studies are yet to be explained.

Olanzapine, quetiapine, and perphenazine treatments were associated with elevations of cholesterol, triglycerides, and fasting glucose levels but not risperidone and ziprasidone. The results with risperidone are surprising because it has been indicated that hyperlipidemia may be a consequence of risperidone treatment also.<sup>11</sup> Risperidone, declared a safe drug by CATIE, has also been shown to

produce abnormal glucose levels<sup>12,13</sup> and increases the risk for diabetes.<sup>13,14</sup> Similarly, although obesity has been noted to be maximum with olanzapine and minimal with risperidone in CATIE trials, other studies with more realistic dosages of risperidone have indicated no differences between the 2, either in clinically significant weight gain<sup>12,14</sup> or in overall weight and body mass index changes.<sup>15</sup> From the previously mentioned arguments, one may conclude that lower dosage of risperidone in the CATIE trial may be responsible for its better adverse-effect profile, which may also be true for ziprasidone.

## DISCUSSION

Unfortunately, even after careful selection of drugs and dosages by CATIE investigators to avoid EPA and prevent TD, the higher rate of atypical antipsychotic-induced MS is alarming. We need to answer several questions that arise here such as: (1) Is it old gold, and do we start preferring typical over atypical antipsychotics to prevent MS? (2) If typical are preferred, what about TD of typical antipsychotics? (3) Can we consider the life-threatening complications of MS to be worse than TD?

These questions need to be addressed urgently in future research on antipsychotic-induced MS. Currently, the long-term effects of MS are comparatively well known in the form of cardiovascular and cerebrovascular disorders, but the long-term effects of antipsychotic-induced MS, which is a recent phenomenon, are not known clearly. Although TD was seen as a disabling effect of older antipsychotics, it was not really life threatening, and other than being cosmetically unacceptable, it was not actually causing any health-related problems. This is unlike MS, which may be considered as a form of neo-TD.<sup>13</sup> Even the course and prognosis of antipsychotic-induced MS are somewhat controversial, especially regarding its reversibility and its dose dependence.<sup>16</sup> We need more research data on the course and outcome of MS before making a final call. It may be preferable to extend the follow-up of CATIE patients. In the interim, patients could be treated with second-generation antipsychotics for first 6 weeks and then switched and maintained on first-generation antipsychotics as soon as risk factors start to develop.<sup>16</sup>

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## Comments on “An Innovative Design to Establish Proof of Concept of the Antidepressant Effects of the NR2B Subunit Selective N-Methyl-D-Aspartate Antagonist, CP-101,606, in Patients With Treatment-Refractory Major Depressive Disorder”

### To the Editors:

I read with great interest the recent article by Preskorn et al<sup>1</sup> about the efficacy of an NR2B subunit-selective N-methyl-D-aspartate (NMDA) receptor antagonist CP-101,606 in treatment-refractory patients with major depressive disorder (MDD). This study was a randomized, double-blind, placebo-controlled study, and this study had 2 treatment periods. In period 1, subjects first received a 6-week open-label trial of paroxetine (20 mg) and a single-blind, intravenous placebo infusion. Period 1 nonresponders (n = 30, defined as  $\leq 20\%$  improvement in the 17-item Hamilton Depression Rating Scale score at the end of period 1 compared with the screening visit) then received a randomized double-blind single infusion of CP-101,606 or placebo plus

continued treatment with paroxetine (40 mg) for up to an additional 4 weeks (period 2). On the prespecified main outcome measure (Montgomery-Åsberg Depression Rating Scale total score at day 5 of period 2), CP-101,606 treatment significantly produced a greater decrease than the placebo group. In addition, Hamilton Depression Rating Scale response was 60% for the CP-101,606-treated group versus 20% for placebo group. Interestingly, 78% of CP-101,606-treated responders maintained response status for at least 1 week after the infusion.<sup>1</sup> There were no deaths or discontinuations due to adverse events or abnormal laboratory findings. Adverse events from the CP-101,606-treated group (n = 15) and the placebo-treated group (n = 15) were 55 and 61 adverse events, respectively. Six patients of the CP-101,606-treated group experienced a dissociative reaction (2 mild, 2 moderate, and 2 severe), and 2 subjects of the placebo-treated group also experienced a mild dissociative reaction. Most adverse events including feeling abnormal, dizziness, paresthesia, somnolence, dry mouth, and abnormal urine odor were mild and did not differ between the CP-101,606-treated group and the placebo-treated groups. These findings suggest that the NR2B subunit of NMDA receptor would be a fruitful target for the development of a new antidepressant with more robust effects and a faster onset compared with those currently available antidepressants.<sup>1</sup>

A growing body of evidence suggests that glutamate plays a key role in the pathophysiology of MDD.<sup>2-5</sup> First, a single dose of the NMDA receptor antagonist ketamine produced a rapid and short-lived antidepressant effect in treatment-refractory patients with MDD.<sup>4</sup> A subsequent double-blind placebo-controlled crossover study found that a single intravenous dose of ketamine (0.5 mg/kg over 40 min) resulted in rapid and significant antidepressant effects in patients with treatment-refractory MDD patients within 2 hours, an effect that remained significant for 7 days.<sup>5</sup> However, the clinical application of ketamine might be limited by its propensity to cause psychotomimetic effects of ketamine.<sup>6</sup>

The NMDA receptors are tetrameric proteins composed of 2 NR1 subunits and 2 NR2 subunits, and 4 different NR2 subunits (NR2A-D) exist in the brain. The NR2B subunit of NMDA receptors is localized primarily in the forebrain including the hippocampus, a region implicated in the pathophysiology of MDD. The NR2B subunit-selective NMDA receptor antagonist CP-101,606 is distinct from that of ketamine, an open-channel blocker

of NMDA receptor. Together, it is likely that the NR2B subtype NMDA receptor antagonists, which do not cause psychotomimetic effects, would be better than those of open-channel blockers (eg, ketamine) of NMDA receptor. CP-101,606 is a derivative of prototypical NR2B subunit-selective drug ifenprodil. We and other group reported that ifenprodil and its derivative CP-101,606 had high to moderate affinity at endoplasmic reticulum protein sigma-1 receptors in the brain<sup>7,8</sup>; which play a role in the pathophysiology of MDD and in the mechanism of antidepressants.<sup>9-11</sup> Therefore, the role of sigma-1 receptors in the mechanism of action of CP-101,606 should be taken into consideration. In the future, it may also be of great interest to study whether or not the selective sigma-1 receptor agonists cause improvement in the treatment-refractory patients with MDD.

#### AUTHOR DISCLOSURE INFORMATION

*The author reports no biomedical financial interests or potential conflicts of interest.*

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#### Reply to Comments by Dr Hashimoto

##### To the Editors:

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